17264

Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Berch Examiner #: 59193 Date: 10/4
Art Unit: 1624 Phone Number 30 8478 Serial Number: 10/080290
Mail Box and Bldg/Room Location: 4D15 / 4E12 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

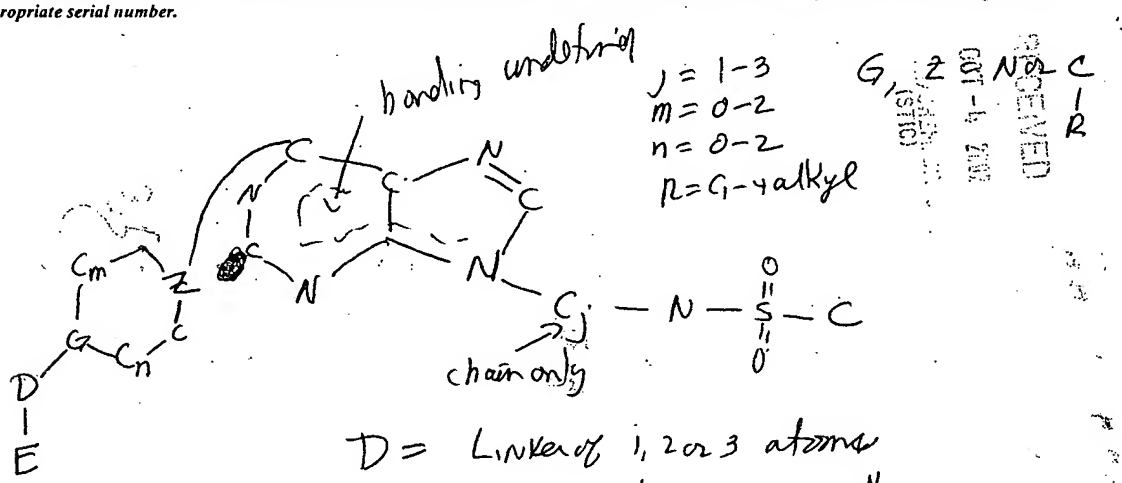
Title of Invention: _____

Inventors (please provide full names): _____

_____

Earliest Priority Filing Date: _____

***For Sequence Searches Only** Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*



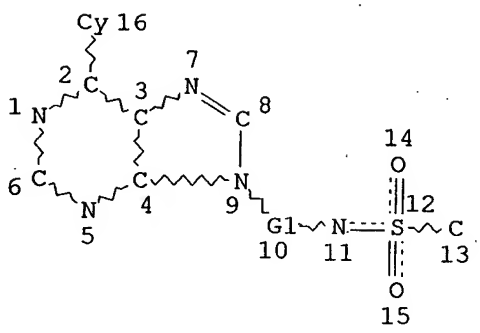
RECEIVED
OCT - 4 2002
TECH CENTER 1600/2900

****

STAFF USE ONLY	**Type of Search**		**Vendors and cost where applicable**
Searcher: _____	NA Sequence (#)_____		STN _____
Searcher Phone #: _____	AA Sequence (#)_____		Dialog _____
Searcher Location: _____	Structure (#) _____		Questel/Orbit _____
Date Searcher Picked Up: _____	Bibliographic _____		Dr.Link _____
Date Completed: _____	Litigation _____		Lexis/Nexis _____
Searcher Prep & Review Time: _____	Fulltext _____		Sequence Systems _____
Clerical Prep Time: _____	Patent Family _____		WWW/Internet _____
Online Time: _____	Other _____		Other (specify)_____

PTO-1590 (8-01)

=> d l3 que stat;d 1-12 ide cbib abs
L1 STR



REP G1=(1-3) C
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED

Searched by: Mary Hale 308-4258 CM-1 1E01

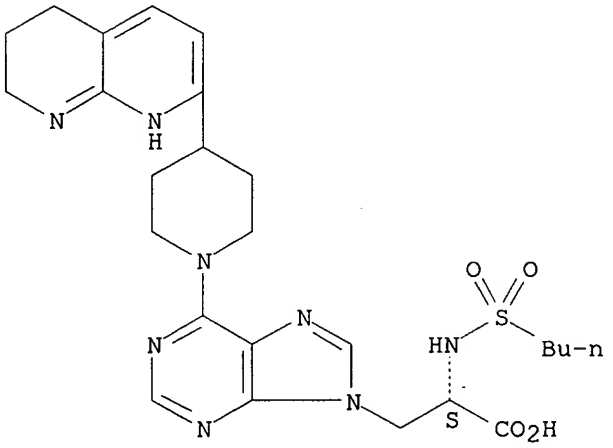
NUMBER OF NODES IS 16

STEREO ATTRIBUTES: NONE
L3 12 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED 146 ITERATIONS 12 ANSWERS
SEARCH TIME: 00.00.02

L3 ANSWER 1 OF 12 REGISTRY COPYRIGHT 2002 ACS
RN 315240-24-5 REGISTRY
CN 9H-Purine-9-propanoic acid, .alpha.-[(butylsulfonyl)amino]-6-[4-(1,5,6,7-tetrahydro-1,8-naphthyridin-2-yl)-1-piperidinyl]-, (.alpha.S)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (2S)-2-(Butane-1-sulfonylamino)-3-(6-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)piperidin-1-yl)purin-9-yl)propionic acid
FS STEREOSEARCH
MF C25 H34 N8 O4 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 134:71600 Naphthyridine derivatives, processes for their preparation, their use as vitronectin receptor antagonists and inhibitors of cell adhesion, and pharmaceutical compositions comprising them. Peyman, Anuschirwan; Scheunemann, Karl-Heinz; Gourvest, Jean-Francois; Ruxer, Jean-Marie; Gadek, Thomas R. (Aventis Pharma Deutschland G.m.b.H., Germany; Genentech, Inc.). Eur. Pat. Appl. EP 1065207 A1 20010103, 36 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL,

Searched by: Mary Hale 308-4258 CM-1 1E01

SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW.
APPLICATION: EP 1999-112636 19990702.

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

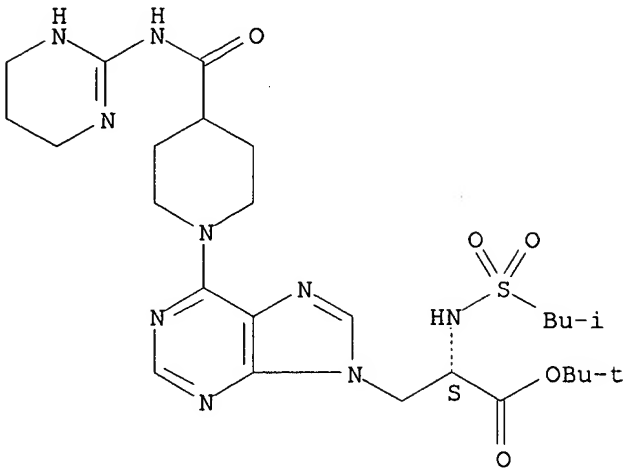
AB The present invention relates to compds. I. G is -(CR1R2)n-A-(CR1R2)m-(CR1R3)i-(CR1R2)q-R4. A is a direct bond, -C(O)NR5-, -NR5C(O)-, -C(O)-, -NR5-, -O-, -S-, -S(O)-, -S(O)2-, (C2-C4)alkynediyl, (C2-C4)alkenediyl, (C5-C14)arylene where in the arylene residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or a divalent residue of a 3-7-membered satd. or unsatd. ring which can contain 1-2 ring heteroatoms N, S and O and which can be monosubstituted or disubstituted by residues :O, :S and R3. B is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl(C1-C8)alkyl, (C5-C14)heteroaryl, (C5-C14)heteroaryl(C1-C8)alkyl, F, Cl, Br, OH, CN, CF3, NO2, CO2H, (C1-C6)alkoxy, (C1-C6)alkoxy(C1-C6)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C5-C14)arylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy(C1-C6)alkoxy, (C5-C14)aryl(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C1-C6)alkylsulfonylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, aminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl(C1-C8)alkylsulfonyl, (C5-C14)aryl or (C5-C14)heteroaryl, where all residues B are independent of one another and can be identical or different. X is H, NR6R6', F, Cl, Br, OR6, SR6, hydroxy(C1-C6)alkyl-NH-, (hydroxy(C1-C6)alkyl)2N-, amino(C1-C6)alkyl-NH-, (amino(C1-C6)alkyl)2N-, hydroxy(C1-C6)alkyl-O-, hydroxy(C1-C6)alkyl-S- or -NH-C(O)-R6. Y is R5, F, Cl, Br, CN, NR6R6', OR6, SR6 or hydroxy(C1-C6)alkyl-NH-. Z is N or CH. R1 and R2 are H, F, Cl, CN, NO2, (C1-C10)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl(C1-C8)alkyl, (C5-C14)heteroaryl, (C5-C14)heteroaryl(C1-C8)alkyl, R6-O-R7, R6-S(O)p-R7, R6S(O)2NHR7, R6OC(O)NHR7 or R6R6'N-R7, where all residues R1 and R2 are independent of one another and can be identical or different. R3 is H, F, Cl, CN, NO2, (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl(C1-C8)alkyl, (C5-C14)heteroaryl, (C5-C14)heteroaryl(C1-C8)alkyl, R6-O-R7, R6R6'N-R7, R6C(O)-O-R7, R6C(O)R7, R6OC(O)R7, R6N(R6')C(O)OR7, R6S(O)pN(R5)R7, R6OC(O)N(R5)R7, R6C(O)N(R5)R7, R6N(R6')C(O)N(R5)R7, R6N(R6')S(O)pN(R5)R7, R6S(O)pR7, R6SC(O)N(R5)R7, R6N(R6')C(O)R7 or R6N(R6')S(O)pR7, where alkyl can be monounsatd. or polyunsatd. and where alkyl, cycloalkyl, aryl, and heteroaryl can be monosubstituted or polysubstituted by R6, F, Cl, Br, CN, CF3, R6R6'NR7, NO2, R6OC(O)R7, R6C(O)R7, R6N(R6')C(O)R7, R6N(R6')S(O)pR7 or R6-O-R7, and where all residues R3 are independent of one another and can be identical or different. R4 is -C(O)R8, -C(S)R8, -S(O)pR8, -P(O)R8R8' or a residue of a 4-8-membered satd. or unsatd. heterocycle which contains 1-4 heteroatoms N, O and S. R5 is H, (C1-C10)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl(C1-C8)alkyl, (C5-C14)aryl or (C5-C14)aryl(C1-C8)alkyl, where all residues R5 are independent of one another and can be identical or different. R6 and R6' are H, (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl(C1-C8)alkyl, (C5-C14)heteroaryl or (C5-C14)heteroaryl(C1-C8)alkyl where aryl, heteroaryl, cycloalkyl and alkyl can be substituted 1-3 times by identical or different substituents F, Cl, Br, CN, CF3, NO2, CO2H, (C1-C6)alkyl, (C1-C6)alkoxy, (C1-C6)alkoxy(C1-C6)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy(C1-C6)alkoxy, (C5-C14)arylcarbonyl, (C5-C14)aryl(C1-C8)alkylcarbonyl,

(C1-C6)alkanoylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, (C1-C6)alkylaminosulfonyl, (C5-C14)arylaminosulfonyl, (C5-C14)aryl(C1-C8)alkylaminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl(C1-C8)alkylsulfonyl, (C5-C14)aryl and (C5-C14)heteroaryl, and where all residues R6 and R6' are independent of one another and can be identical or different. R7 is (C1-C4)alkanediyl or a direct bond, where all residues R7 are independent of one another and can be identical or different. R8 and R8' are OH, (C1-C8)alkoxy, (C5-C14)aryl(C1-C8)alkoxy, (C5-C14)aryloxy, (C1-C8)alkylcarbonyloxy(C1-C4)alkoxy, (C5-C14)aryl(C1-C8)alkylcarbonyloxy(C1-C8)alkoxy, NR6R6', (di((C1-C8)alkyl) amino)carbonylmethyloxy, (di((C5-C14)aryl(C1-C8)alkyl)amino)carbonylmethyloxy, (C5-C14)arylamino, the residue of an amino acid, N-((C1-C4)alkyl)piperidin-4-yloxy, 2-methylsulfonylethoxy, 1,3-thiazol-2-ylmethyloxy, 3-pyridylmethyloxy, 2-(di((C1-C4)alkyl)amino)ethoxy or the residue Q-(CH3)3N+-CH2-CH2-O- in which Q- is a physiol. tolerable anion, where all residues R8 and R8' are independent of one another and can be identical or different. N is 0-5; m is 0-5; i is 0-1; q is 0-2; r is 0-2; s is 0-3; t is 0-8; p is 0-2, where all nos. p are independent of one another and can be identical or different. The claimed compds. also include stereoisomeric forms and mixts. thereof in all ratios, and their physiol. tolerable salts and their prodrugs; where, instead of the purine structure shown I, also a 3-deazapurine structure, a 7-deazapurine structure or a 7-deaza-8-azapurine structure can be present. I are valuable pharmacol. active compds. They are vitronectin receptor antagonists and inhibitors of cell adhesion and are suitable for the therapy and prophylaxis of illnesses which are based on the interaction between vitronectin receptors and their ligands in cell-cell or cell-matrix interaction processes or which can be prevented, alleviated or cured by influencing such interactions. For example, they can be applied for inhibiting bone resorption by osteoclasts and thus for treating and preventing osteoporosis, or for inhibiting undesired angiogenesis or proliferation of cells of the vascular smooth musculature. The invention furthermore relates to processes for the prepn. of I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical compns. comprising them. The process of prepn. comprises reacting II (L1 = leaving group) with III or IV; B, G, X, Y, r, s and t are defined as above but wherein functional groups can also be present in the form of precursor groups or in protected form. For example, (2S)-2-benzyloxycarbonylamino-3-(6-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)piperidin-1-yl)purin-9-yl)propionic acid tert-Bu ester could be made from 7-(piperidin-4-yl)-1,2,3,4-tetrahydro-1,8-naphthyridine and (S)-2-benzyloxycarbonylamino-3-(6-chloropurin-9-yl)propionic acid tert-Bu ester in DMF in the presence of NEtiPr2; the ester was then hydrolyzed by CF3CO2H to give the desired compd.

L3 ANSWER 2 OF 12 REGISTRY COPYRIGHT 2002 ACS
RN 315212-44-3 REGISTRY
CN 9H-Purine-9-propanoic acid, .alpha.-[[(2-methylpropyl)sulfonyl]amino]-6-[4-[[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]carbonyl]-1-piperidinyl]-, 1,1-dimethylethyl ester, (.alpha.S)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (2S)-2-(2-Methylpropane-1-sulfonylamino)-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid tert-butyl ester
FS STEREOSEARCH
MF C26 H41 N9 O5 S
SR CA
LC STN Files: CA, CAPLUS

Searched by: Mary Hale 308-4258 CM-1 1E01

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 134:71601 Substituted purine derivatives, method of preparation and use as inhibitors of cell adhesion. Knolle, Jochen; Peyman, Anuschirwan; Gourvest, Jean-Francois; Ruxer, Jean-Marie; Gadek, Thomas R. (Aventis Pharma Deutschland G.m.b.H., Germany; Genentech, Inc.). Eur. Pat. Appl. EP 1065208 A1 20010103, 41 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 1999-112637 19990702.

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention relates to purine derivs. I. B is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl, (C5-C14)heteroaryl-(C1-C8)alkyl, F, Cl, Br, OH, CN, CF3, NO2, CO2H, (C1-C6)alkoxy, (C1-C6)alkoxy-(C1-C6)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C5-C14)arylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C1-C6)alkylsulfonylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, aminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl or (C5-C14)heteroaryl, where all residues B are independent of one another and can be identical or different, or B denotes an arom. or nonarom. ring system that is fused to the 6-membered ring contg. the groups G and Z. D is -C(O)-N(R6)-, -NR6-C(O)-, -NR6-C(O)-N(R6)-, -NR6-C(S)-N(R6)-, -C(S)-N(R6)- or -C(R6):N-N(R6)-, where the divalent residues representing D are bonded to the group E via the free bond on their right side. E is a residue from the series consisting of possibly substituted 2-pyrimidinyl, . pyrrolyl, 2-imidazolyl, 2-imidazolin-2-yl, 2-pyridinyl many other N

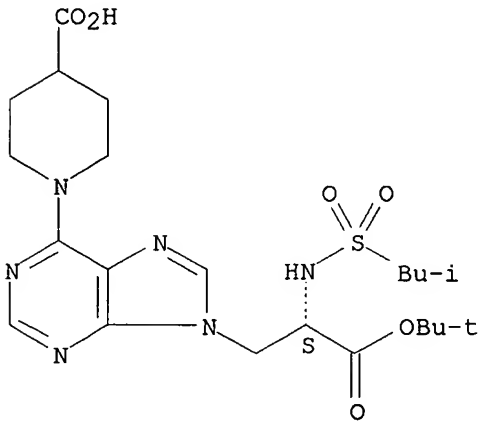
Searched by: Mary Hale 308-4258 CM-1 1E01

heterocycles, R6-C(:NR6)-NR6-, and R6R6'N-C(:NR6)-. G is N, CH or C((C1-C4)alkyl). X is H, -NR6R6', F, Cl, Br, -OR6, -SR6, hydroxy-(C1-C6)alkyl-NH-, (hydroxy-(C1-C6)alkyl)2N-, amino-(C1-C6)alkyl-NH-, (amino-(C1-C6)alkyl)2N-, hydroxy-(C1-C6)alkyl-O-, hydroxy-(C1-C6)alkyl-S- or -NH-C(O)-R6. Y has one of the meanings of R6 or is F, Cl, Br, CN, -NR6R6', -OR6, -SR6 or hydroxy-(C1-C6)alkyl-NH-. Z is N or CH. R1 is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl or (C5-C14)heteroaryl-(C1-C8)alkyl, where aryl, heteroaryl, cycloalkyl and alkyl can be substituted one, two or three times by identical or different substituents from the series consisting of F, Cl, Br, CN, CF3, NO2, CO2H, (C1-C6)alkyl, (C1-C6)alkoxy, (C1-C6)alkoxy-(C1-C8)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, (C1-C6)alkylaminosulfonyl, (C5-C14)arylaminosulfonyl, (C5-C14)aryl-(C1-C8)alkylaminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl and (C5-C14)heteroaryl. R2 is -C(O)R5, -C(S)R5, -S(O)pR5, -P(O)R5R5' or a residue of a 4-membered to 8-membered satd. or unsatd. heterocycle which contains 1-4 heteroatoms from the series consisting of N, O and S. R5 and R5' are OH, (C1-C8)alkoxy, (C5-C14)aryl-(C1-C8)alkoxy, (C1-C8)alkylcarbonyloxy-(C1-C4)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyloxy(C1-C8)alkoxy- or -NR6R6', where the residues R5' and R5' are independent of one another and can be identical or different. R6 and R6' are H, (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl where in the aryl residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or (C5-C14)aryl-(C1-C8)alkyl, where in the aryl moiety of the arylalkyl residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or R6 and R6' together with the N atom to which they are bonded form a 4-8-membered ring system which in addn. to the N atom to which R6 and R6' are bonded can contain 1-3 ring heteroatoms N, O and S and which can be unsatd. or satd., where all residues R6 and R6' are independent of one another and can be identical or different. R = 0-4; s = 0-4; v = 1-3; p = 1-2. The present invention also relates to stereoisomeric forms and mixts. thereof in all ratios, and their physiol. tolerable salts and their prodrugs; where, instead of the purine structure shown in I, also a 3-deazapurine structure, a 7-deazapurine structure or a 7-deaza-8-azapurine structure can be present. I are valuable pharmacol. active compds. They are vitronectin receptor antagonists and inhibitors of cell adhesion and are suitable for the therapy and prophylaxis of illnesses which are based on the interaction between vitronectin receptors and their ligands in cell-cell or cell-matrix interaction processes or which can be prevented, alleviated or cured by influencing such interactions. For example, they can be applied for inhibiting bone resorption by osteoclasts and thus for treating and preventing osteoporosis, or for inhibiting undesired angiogenesis or proliferation of cells of the vascular smooth musculature. The invention furthermore relates to processes for the prepn. of I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical compns. comprising them. The process for the prepn. comprises reacting II (L1 = leaving group; R15 = R1SO2 or an amino protecting group) with III or IV; B, D, E, G, X, R2 and s are as defined above but functional groups can also be present in the form of precursor groups or in protected form. For example, (2S)-2-benzyloxycarbonylamino-3-(6-chloropurin-9-yl)propionic acid tert-Bu ester was reacted with piperidine-4-carboxylic acid in the presence of N,O-bis(trimethylsilyl)acetamide to give 1-(9-((2S)-2-benzyloxycarbonylamino-2-tert-butoxycarbonylethyl)purin-6-yl)piperidine-4-carboxylic acid, which was reacted with 2-amino-1,4,5,6-

tetrahydropyrimidine hydrochloride to give (2S)-2-Benzyloxycarbonylamino-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid tert-Bu ester, which was deprotected at N, N-sulfonated by various sulfonyl chlorides and hydrolyzed to give products such as (2S)-2-(naphthalene-1-sulfonylamino)-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid.

L3 ANSWER 3 OF 12 REGISTRY COPYRIGHT 2002 ACS
RN 315212-43-2 REGISTRY
CN 9H-Purine-9-propanoic acid, 6-(4-carboxy-1-piperidinyl)-.alpha.-[[(2-methylpropyl)sulfonyl]amino]-, .alpha.-(1,1-dimethylethyl) ester, (.alpha.S)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1-(9-((2S)-2-tert-Butoxycarbonyl-2-(2-methylpropane-1-sulfonylamino)ethyl)purin-6-yl)piperidine-4-carboxylic acid
FS STEREOSEARCH
MF C22 H34 N6 O6 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 134:71601 Substituted purine derivatives, method of preparation and use as inhibitors of cell adhesion. Knolle, Jochen; Peyman, Anuschirwan; Gourvest, Jean-Francois; Ruxer, Jean-Marie; Gadek, Thomas R. (Aventis Pharma Deutschland G.m.b.H., Germany; Genentech, Inc.). Eur. Pat. Appl. EP 1065208 A1 20010103, 41 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 1999-112637 19990702.
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention relates to purine derivs. I. B is (C1-C18)alkyl,

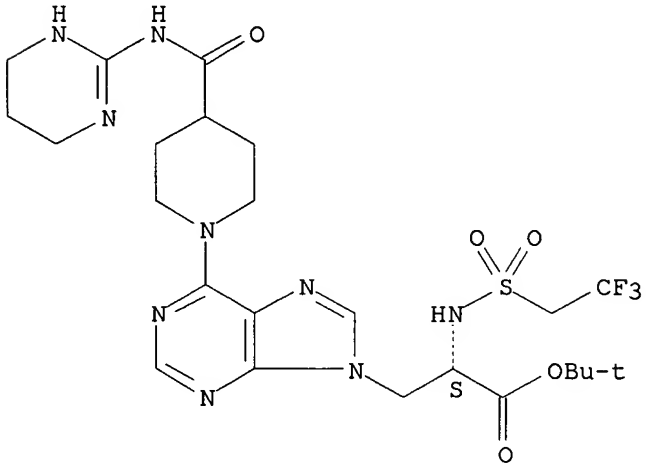
Searched by: Mary Hale 308-4258 CM-1 1E01

(C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl, (C5-C14)heteroaryl-(C1-C8)alkyl, F, Cl, Br, OH, CN, CF3, NO2, CO2H, (C1-C6)alkoxy, (C1-C6)alkoxy-(C1-C6)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C5-C14)arylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C1-C6)alkylsulfonylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, aminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl or (C5-C14)heteroaryl, where all residues B are independent of one another and can be identical or different, or B denotes an arom. or nonarom. ring system that is fused to the 6-membered ring contg. the groups G and Z. D is -C(O)-N(R6)-, -NR6-C(O)-, -NR6-C(O)-N(R6)-, -NR6-C(S)-N(R6)-, -C(S)-N(R6)- or -C(R6):N-N(R6)-, where the divalent residues representing D are bonded to the group E via the free bond on their right side. E is a residue from the series consisting of possibly substituted 2-pyrimidinyl, pyrrolyl, 2-imidazolyl, 2-imidazolin-2-yl, 2-pyridinyl many other N heterocycles, R6-C(:NR6)-NR6-, and R6R6'N-C(:NR6)-. G is N, CH or C((C1-C4)alkyl). X is H, -NR6R6', F, Cl, Br, -OR6, -SR6, hydroxy-(C1-C6)alkyl-NH-, (hydroxy-(C1-C6)alkyl)2N-, amino-(C1-C6)alkyl-NH-, (amino-(C1-C6)alkyl)2N-, hydroxy-(C1-C6)alkyl-O-, hydroxy-(C1-C6)alkyl-S- or -NH-C(O)-R6. Y has one of the meanings of R6 or is F, Cl, Br, CN, -NR6R6', -OR6, -SR6 or hydroxy-(C1-C6)alkyl-NH-. Z is N or CH. R1 is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl or (C5-C14)heteroaryl-(C1-C8)alkyl, where aryl, heteroaryl, cycloalkyl and alkyl can be substituted one, two or three times by identical or different substituents from the series consisting of F, Cl, Br, CN, CF3, NO2, CO2H, (C1-C6)alkyl, (C1-C6)alkoxy, (C1-C6)alkoxy-(C1-C8)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, (C1-C6)alkylaminosulfonyl, (C5-C14)arylaminosulfonyl, (C5-C14)aryl-(C1-C8)alkylaminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl and (C5-C14)heteroaryl. R2 is -C(O)R5, -C(S)R5, -S(O)pR5, -P(O)R5R5' or a residue of a 4-membered to 8-membered satd. or unsatd. heterocycle which contains 1-4 heteroatoms from the series consisting of N, O and S. R5 and R5' are OH, (C1-C8)alkoxy, (C5-C14)aryl-(C1-C8)alkoxy, (C1-C8)alkylcarbonyloxy-(C1-C4)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyloxy(C1-C8)alkoxy- or -NR6R6', where the residues R5' and R5' are independent of one another and can be identical or different. R6 and R6' are H, (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl where in the aryl residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or (C5-C14)aryl-(C1-C8)alkyl, where in the aryl moiety of the arylalkyl residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or R6 and R6' together with the N atom to which they are bonded form a 4-8-membered ring system which in addn. to the N atom to which R6 and R6' are bonded can contain 1-3 ring heteroatoms N, O and S and which can be unsatd. or satd., where all residues R6 and R6' are independent of one another and can be identical or different. R = 0-4; s = 0-4; v = 1-3; p = 1-2. The present invention also relates to stereoisomeric forms and mixts. thereof in all ratios, and their physiol. tolerable salts and their prodrugs; where, instead of the purine structure shown in I, also a 3-deazapurine structure, a 7-deazapurine structure or a 7-deaza-8-azapurine structure can be present. I are valuable pharmacol. active compds. They are vitronectin receptor antagonists and inhibitors of cell adhesion and are suitable for the therapy and prophylaxis of illnesses which are based on the interaction between vitronectin receptors

and their ligands in cell-cell or cell-matrix interaction processes or which can be prevented, alleviated or cured by influencing such interactions. For example, they can be applied for inhibiting bone resorption by osteoclasts and thus for treating and preventing osteoporosis, or for inhibiting undesired angiogenesis or proliferation of cells of the vascular smooth musculature. The invention furthermore relates to processes for the prepn. of I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical compns. comprising them. The process for the prepn. comprises reacting II (L1 = leaving group; R15 = R1SO2 or an amino protecting group) with III or IV; B, D, E, G, X, R2 and s are as defined above but functional groups can also be present in the form of precursor groups or in protected form. For example, (2S)-2-benzyloxycarbonylamino-3-(6-chloropurin-9-yl)propionic acid tert-Bu ester was reacted with piperidine-4-carboxylic acid in the presence of N,O-bis(trimethylsilyl)acetamide to give 1-(9-((2S)-2-benzyloxycarbonylamino-2-tert-butoxycarbonylethyl)purin-6-yl)piperidine-4-carboxylic acid, which was reacted with 2-amino-1,4,5,6-tetrahydropyrimidine hydrochloride to give (2S)-2-Benzyloxycarbonylamino-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid tert-Bu ester, which was deprotected at N, N-sulfonated by various sulfonyl chlorides and hydrolyzed to give products such as (2S)-2-(naphthalene-1-sulfonylamino)-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid.

L3 ANSWER 4 OF 12 REGISTRY COPYRIGHT 2002 ACS
RN 315212-41-0 REGISTRY
CN 9H-Purine-9-propanoic acid, 6-[4-[[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]carbonyl]-1-piperidinyl]-.alpha.-[[(2,2,2-trifluoroethyl)sulfonyl]amino]-, 1,1-dimethylethyl ester, (.alpha.S)-(9CI) (CA INDEX NAME)
OTHER NAMES:
CN (2S)-3-(6-(4-(1,4,5,6-Tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)-2-(2,2,2-trifluoroethanesulfonylamino)propionic acid tert-butyl ester
FS STEREOSEARCH
MF C24 H34 F3 N9 O5 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



Searched by: Mary Hale 308-4258 CM-1 1E01

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 134:71601 Substituted purine derivatives, method of preparation and use as inhibitors of cell adhesion. Knolle, Jochen; Peyman, Anuschirwan; Gourvest, Jean-Francois; Ruxer, Jean-Marie; Gadek, Thomas R. (Aventis Pharma Deutschland G.m.b.H., Germany; Genentech, Inc.). Eur. Pat. Appl. EP 1065208 A1 20010103, 41 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 1999-112637 19990702.

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

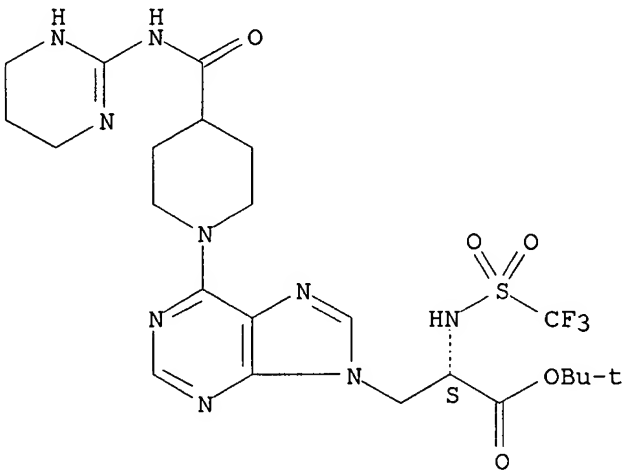
AB The present invention relates to purine derivs. I. B is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl, (C5-C14)heteroaryl-(C1-C8)alkyl, F, Cl, Br, OH, CN, CF3, NO2, CO2H, (C1-C6)alkoxy, (C1-C6)alkoxy-(C1-C6)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C5-C14)arylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C1-C6)alkylsulfonylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, aminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl or (C5-C14)heteroaryl, where all residues B are independent of one another and can be identical or different, or B denotes an arom. or nonarom. ring system that is fused to the 6-membered ring contg. the groups G and Z. D is -C(O)-N(R6)-, -NR6-C(O)-, -NR6-C(O)-N(R6)-, -NR6-C(S)-N(R6)-, -C(S)-N(R6)- or -C(R6):N-N(R6)-, where the divalent residues representing D are bonded to the group E via the free bond on their right side. E is a residue from the series consisting of possibly substituted 2-pyrimidinyl, pyrrolyl, 2-imidazolyl, 2-imidazolin-2-yl, 2-pyridinyl many other N heterocycles, R6-C(:NR6)-NR6-, and R6R6'N-C(:NR6)-. G is N, CH or C((C1-C4)alkyl). X is H, -NR6R6', F, Cl, Br, -OR6, -SR6, hydroxy-(C1-C6)alkyl-NH-, (hydroxy-(C1-C6)alkyl)2N-, amino-(C1-C6)alkyl-NH-, (amino-(C1-C6)alkyl)2N-, hydroxy-(C1-C6)alkyl-O-, hydroxy-(C1-C6)alkyl-S- or -NH-C(O)-R6. Y has one of the meanings of R6 or is F, Cl, Br, CN, -NR6R6', -OR6, -SR6 or hydroxy-(C1-C6)alkyl-NH-. Z is N or CH. R1 is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl or (C5-C14)heteroaryl-(C1-C8)alkyl, where aryl, heteroaryl, cycloalkyl and alkyl can be substituted one, two or three times by identical or different substituents from the series consisting of F, Cl, Br, CN, CF3, NO2, CO2H, (C1-C6)alkyl, (C1-C6)alkoxy, (C1-C6)alkoxy-(C1-C8)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, (C1-C6)alkylaminosulfonyl, (C5-C14)arylaminosulfonyl, (C5-C14)aryl-(C1-C8)alkylaminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl and (C5-C14)heteroaryl. R2 is -C(O)R5, -C(S)R5, -S(O)pR5, -P(O)R5R5' or a residue of a 4-membered to 8-membered satd. or unsatd. heterocycle which

contains 1-4 heteroatoms from the series consisting of N, O and S. R5 and R5' are OH, (C1-C8)alkoxy, (C5-C14)aryl-(C1-C8)alkoxy, (C1-C8)alkylcarbonyloxy-(C1-C4)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyloxy(C1-C8)alkoxy- or -NR6R6', where the residues R5' and R5' are independent of one another and can be identical or different. R6 and R6' are H, (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl where in the aryl residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or (C5-C14)aryl-(C1-C8)alkyl, where in the aryl moiety of the arylalkyl residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or R6 and R6' together with the N atom to which they are bonded form a 4-8-membered ring system which in addn. to the N atom to which R6 and R6' are bonded can contain 1-3 ring heteroatoms N, O and S and which can be unsatd. or satd., where all residues R6 and R6' are independent of one another and can be identical or different. R = 0-4; s = 0-4; v = 1-3; p = 1-2. The present invention also relates to stereoisomeric forms and mixts. thereof in all ratios, and their physiol. tolerable salts and their prodrugs; where, instead of the purine structure shown in I, also a 3-deazapurine structure, a 7-deazapurine structure or a 7-deaza-8-azapurine structure can be present. I are valuable pharmacol. active compds. They are vitronectin receptor antagonists and inhibitors of cell adhesion and are suitable for the therapy and prophylaxis of illnesses which are based on the interaction between vitronectin receptors and their ligands in cell-cell or cell-matrix interaction processes or which can be prevented, alleviated or cured by influencing such interactions. For example, they can be applied for inhibiting bone resorption by osteoclasts and thus for treating and preventing osteoporosis, or for inhibiting undesired angiogenesis or proliferation of cells of the vascular smooth musculature. The invention furthermore relates to processes for the prepn. of I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical compns. comprising them. The process for the prepn. comprises reacting II (L1 = leaving group; R15 = R1SO2 or an amino protecting group) with III or IV; B, D, E, G, X, R2 and s are as defined above but functional groups can also be present in the form of precursor groups or in protected form. For example, (2S)-2-benzyloxycarbonylamino-3-(6-chloropurin-9-yl)propionic acid tert-Bu ester was reacted with piperidine-4-carboxylic acid in the presence of N,O-bis(trimethylsilyl)acetamide to give 1-(9-((2S)-2-benzyloxycarbonylamino-2-tert-butoxycarbonylethyl)purin-6-yl)piperidine-4-carboxylic acid, which was reacted with 2-amino-1,4,5,6-tetrahydropyrimidine hydrochloride to give (2S)-2-Benzyloxycarbonylamino-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid tert-Bu ester, which was deprotected at N, N-sulfonated by various sulfonyl chlorides and hydrolyzed to give products such as (2S)-2-(naphthalene-1-sulfonylamino)-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid.

L3 ANSWER 5 OF 12 REGISTRY COPYRIGHT 2002 ACS
RN 315212-40-9 REGISTRY
CN 9H-Purine-9-propanoic acid, 6-[4-[[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]carbonyl]-1-piperidinyl]-.alpha.-[[(trifluoromethyl)sulfonyl]amino]-, 1,1-dimethylethyl ester, (.alpha.S)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (2S)-3-(6-(4-(1,4,5,6-Tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)-2-trifluoromethanesulfonylaminopropionic acid tert-butyl ester
FS STEREOSEARCH
MF C23 H32 F3 N9 O5 S
SR CA
LC STN Files: CA, CAPLUS

Searched by: Mary Hale 308-4258 CM-1 1E01

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 134:71601 Substituted purine derivatives, method of preparation and use as inhibitors of cell adhesion. Knolle, Jochen; Peyman, Anuschirwan; Gourvest, Jean-Francois; Ruxer, Jean-Marie; Gadek, Thomas R. (Aventis Pharma Deutschland G.m.b.H., Germany; Genentech, Inc.). Eur. Pat. Appl. EP 1065208 A1 20010103, 41 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 1999-112637 19990702.

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention relates to purine derivs. I. B is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl, (C5-C14)heteroaryl-(C1-C8)alkyl, F, Cl, Br, OH, CN, CF3, NO2, CO2H, (C1-C6)alkoxy, (C1-C6)alkoxy-(C1-C6)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C5-C14)arylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C1-C6)alkylsulfonylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, aminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl or (C5-C14)heteroaryl, where all residues B are independent of one another and can be identical or different, or B denotes an arom. or nonarom. ring system that is fused to the 6-membered ring contg. the groups G and Z. D is -C(O)-N(R6)-, -NR6-C(O)-, -NR6-C(O)-N(R6)-, -NR6-C(S)-N(R6)-, -C(S)-N(R6)- or -C(R6):N-N(R6)-, where the divalent residues representing D are bonded to the group E via the free bond on their right side. E is a residue from the series consisting of possibly substituted 2-pyrimidinyl,

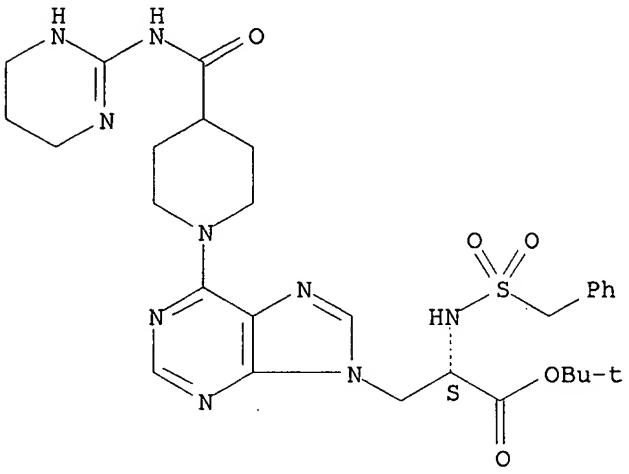
Searched by: Mary Hale 308-4258 CM-1 1E01

pyrrolyl, 2-imidazolyl, 2-imidazolin-2-yl, 2-pyridinyl many other N heterocycles, R6-C(:NR6)-NR6-, and R6R6'N-C(:NR6)-. G is N, CH or C((C1-C4)alkyl). X is H, -NR6R6', F, Cl, Br, -OR6, -SR6, hydroxy-(C1-C6)alkyl-NH-, (hydroxy-(C1-C6)alkyl)2N-, amino-(C1-C6)alkyl-NH-, (amino-(C1-C6)alkyl)2N-, hydroxy-(C1-C6)alkyl-O-, hydroxy-(C1-C6)alkyl-S- or -NH-C(O)-R6. Y has one of the meanings of R6 or is F, Cl, Br, CN, -NR6R6', -OR6, -SR6 or hydroxy-(C1-C6)alkyl-NH-. Z is N or CH. R1 is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl or (C5-C14)heteroaryl-(C1-C8)alkyl, where aryl, heteroaryl, cycloalkyl and alkyl can be substituted one, two or three times by identical or different substituents from the series consisting of F, Cl, Br, CN, CF3, NO2, CO2H, (C1-C6)alkyl, (C1-C6)alkoxy, (C1-C6)alkoxy-(C1-C8)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, (C1-C6)alkylaminosulfonyl, (C5-C14)arylaminosulfonyl, (C5-C14)aryl-(C1-C8)alkylaminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl and (C5-C14)heteroaryl. R2 is -C(O)R5, -C(S)R5, -S(O)pR5, -P(O)R5R5' or a residue of a 4-membered to 8-membered satd. or unsatd. heterocycle which contains 1-4 heteroatoms from the series consisting of N, O and S. R5 and R5' are OH, (C1-C8)alkoxy, (C5-C14)aryl-(C1-C8)alkoxy, (C1-C8)alkylcarbonyloxy-(C1-C4)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyloxy(C1-C8)alkoxy- or -NR6R6', where the residues R5' and R5' are independent of one another and can be identical or different. R6 and R6' are H, (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl where in the aryl residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or (C5-C14)aryl-(C1-C8)alkyl, where in the aryl moiety of the arylalkyl residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or R6 and R6' together with the N atom to which they are bonded form a 4-8-membered ring system which in addn. to the N atom to which R6 and R6' are bonded can contain 1-3 ring heteroatoms N, O and S and which can be unsatd. or satd., where all residues R6 and R6' are independent of one another and can be identical or different. R = 0-4; s = 0-4; v = 1-3; p = 1-2. The present invention also relates to stereoisomeric forms and mixts. thereof in all ratios, and their physiol. tolerable salts and their prodrugs; where, instead of the purine structure shown in I, also a 3-deazapurine structure, a 7-deazapurine structure or a 7-deaza-8-azapurine structure can be present. I are valuable pharmacol. active compds. They are vitronectin receptor antagonists and inhibitors of cell adhesion and are suitable for the therapy and prophylaxis of illnesses which are based on the interaction between vitronectin receptors and their ligands in cell-cell or cell-matrix interaction processes or which can be prevented, alleviated or cured by influencing such interactions. For example, they can be applied for inhibiting bone resorption by osteoclasts and thus for treating and preventing osteoporosis, or for inhibiting undesired angiogenesis or proliferation of cells of the vascular smooth musculature. The invention furthermore relates to processes for the prepn. of I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical compns. comprising them. The process for the prepn. comprises reacting II (L1 = leaving group; R15 = R1SO2 or an amino protecting group) with III or IV; B, D, E, G, X, R2 and s are as defined above but functional groups can also be present in the form of precursor groups or in protected form. For example, (2S)-2-benzyloxycarbonylamino-3-(6-chloropurin-9-yl)propionic acid tert-Bu ester was reacted with piperidine-4-carboxylic acid in the presence of N,O-bis(trimethylsilyl)acetamide to give 1-(9-((2S)-2-benzyloxycarbonylamino-2-tert-butoxycarbonylethyl)purin-6-yl)piperidine-4-

carboxylic acid, which was reacted with 2-amino-1,4,5,6-tetrahydropyrimidine hydrochloride to give (2S)-2-Benzyloxycarbonylamino-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid tert-Bu ester, which was deprotected at N, N-sulfonated by various sulfonyl chlorides and hydrolyzed to give products such as (2S)-2-(naphthalene-1-sulfonylamino)-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid.

L3 ANSWER 6 OF 12 REGISTRY COPYRIGHT 2002 ACS
RN 315212-39-6 REGISTRY
CN 9H-Purine-9-propanoic acid, .alpha.-[[(phenylmethyl)sulfonyl]amino]-6-[4-[[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]carbonyl]-1-piperidinyl]-, 1,1-dimethylethyl ester, (.alpha.S)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (2S)-2-Phenylmethanesulfonylamino-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid tert-butyl ester
FS STEREOSEARCH
MF C29 H39 N9 O5 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 134:71601 Substituted purine derivatives, method of preparation and use as inhibitors of cell adhesion. Knolle, Jochen; Peyman, Anuschirwan; Gourvest, Jean-Francois; Ruxer, Jean-Marie; Gadek, Thomas R. (Aventis Pharma Deutschland G.m.b.H., Germany; Genentech, Inc.). Eur. Pat. Appl. EP 1065208 A1 20010103, 41 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 1999-112637 19990702.
GI

Searched by: Mary Hale 308-4258 CM-1 1E01

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

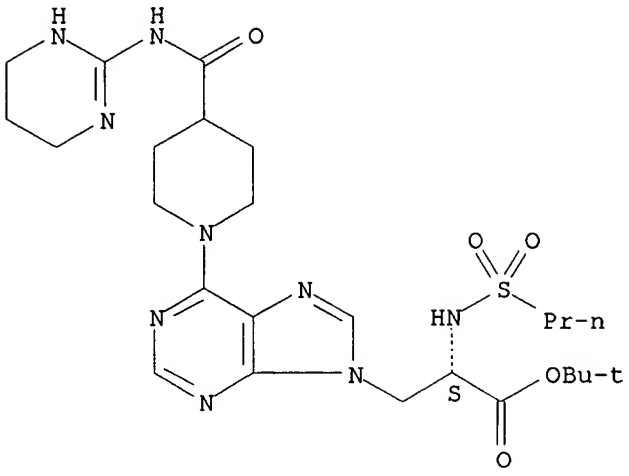
AB The present invention relates to purine derivs. I. B is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl, (C5-C14)heteroaryl-(C1-C8)alkyl, F, Cl, Br, OH, CN, CF3, NO2, CO2H, (C1-C6)alkoxy, (C1-C6)alkoxy-(C1-C6)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C5-C14)arylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C1-C6)alkylsulfonylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, aminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl or (C5-C14)heteroaryl, where all residues B are independent of one another and can be identical or different, or B denotes an arom. or nonarom. ring system that is fused to the 6-membered ring contg. the groups G and Z. D is -C(O)-N(R6)-, -NR6-C(O)-, -NR6-C(O)-N(R6)-, -NR6-C(S)-N(R6)-, -C(S)-N(R6)- or -C(R6):N-N(R6)-, where the divalent residues representing D are bonded to the group E via the free bond on their right side. E is a residue from the series consisting of possibly substituted 2-pyrimidinyl, pyrrolyl, 2-imidazolyl, 2-imidazolin-2-yl, 2-pyridinyl many other N heterocycles, R6-C(:NR6)-NR6-, and R6R6'N-C(:NR6)-. G is N, CH or C((C1-C4)alkyl). X is H, -NR6R6', F, Cl, Br, -OR6, -SR6, hydroxy-(C1-C6)alkyl-NH-, (hydroxy-(C1-C6)alkyl)2N-, amino-(C1-C6)alkyl-NH-, (amino-(C1-C6)alkyl)2N-, hydroxy-(C1-C6)alkyl-O-, hydroxy-(C1-C6)alkyl-S- or -NH-C(O)-R6. Y has one of the meanings of R6 or is F, Cl, Br, CN, -NR6R6', -OR6, -SR6 or hydroxy-(C1-C6)alkyl-NH-. Z is N or CH. R1 is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl or (C5-C14)heteroaryl-(C1-C8)alkyl, where aryl, heteroaryl, cycloalkyl and alkyl can be substituted one, two or three times by identical or different substituents from the series consisting of F, Cl, Br, CN, CF3, NO2, CO2H, (C1-C6)alkyl, (C1-C6)alkoxy, (C1-C6)alkoxy-(C1-C8)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, (C1-C6)alkylaminosulfonyl, (C5-C14)arylaminosulfonyl, (C5-C14)aryl-(C1-C8)alkylaminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl and (C5-C14)heteroaryl. R2 is -C(O)R5, -C(S)R5, -S(O)pR5, -P(O)R5R5' or a residue of a 4-membered to 8-membered satd. or unsatd. heterocycle which contains 1-4 heteroatoms from the series consisting of N, O and S. R5 and R5' are OH, (C1-C8)alkoxy, (C5-C14)aryl-(C1-C8)alkoxy, (C1-C8)alkylcarbonyloxy-(C1-C4)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyloxy(C1-C8)alkoxy- or -NR6R6', where the residues R5' and R5' are independent of one another and can be identical or different. R6 and R6' are H, (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl where in the aryl residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or (C5-C14)aryl-(C1-C8)alkyl, where in the aryl moiety of the arylalkyl residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or R6 and R6' together with the N atom to which they are bonded form a 4-8-membered ring system which in addn. to the N atom to which R6 and R6' are bonded can contain 1-3 ring heteroatoms N, O and S and which can be unsatd. or satd., where all residues R6 and R6' are independent of one another and can be identical or different. R = 0-4; s = 0-4; v = 1-3; p = 1-2. The present invention also relates to stereoisomeric forms and mixts. thereof in all ratios, and their physiol. tolerable salts and their prodrugs; where, instead of the purine structure shown in I, also a 3-deazapurine structure, a 7-deazapurine structure or a

7-deaza-8-azapurine structure can be present. I are valuable pharmacol. active compds. They are vitronectin receptor antagonists and inhibitors of cell adhesion and are suitable for the therapy and prophylaxis of illnesses which are based on the interaction between vitronectin receptors and their ligands in cell-cell or cell-matrix interaction processes or which can be prevented, alleviated or cured by influencing such interactions. For example, they can be applied for inhibiting bone resorption by osteoclasts and thus for treating and preventing osteoporosis, or for inhibiting undesired angiogenesis or proliferation of cells of the vascular smooth musculature. The invention furthermore relates to processes for the prepn. of I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical compns. comprising them. The process for the prepn. comprises reacting II (L1 = leaving group; R15 = R1SO2 or an amino protecting group) with III or IV; B, D, E, G, X, R2 and s are as defined above but functional groups can also be present in the form of precursor groups or in protected form. For example, (2S)-2-benzyloxycarbonylamino-3-(6-chloropurin-9-yl)propionic acid tert-Bu ester was reacted with piperidine-4-carboxylic acid in the presence of N,O-bis(trimethylsilyl)acetamide to give 1-(9-((2S)-2-benzyloxycarbonylamino-2-tert-butoxycarbonylethyl)purin-6-yl)piperidine-4-carboxylic acid, which was reacted with 2-amino-1,4,5,6-tetrahydropyrimidine hydrochloride to give (2S)-2-Benzyloxycarbonylamino-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid tert-Bu ester, which was deprotected at N, N-sulfonated by various sulfonyl chlorides and hydrolyzed to give products such as (2S)-2-(naphthalene-1-sulfonylamino)-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid.

L3 ANSWER 7 OF 12 REGISTRY COPYRIGHT 2002 ACS
RN 315212-36-3 REGISTRY
CN 9H-Purine-9-propanoic acid, .alpha.-[(propylsulfonyl)amino]-6-[4-[[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]carbonyl]-1-piperidinyl]-, 1,1-dimethylethyl ester, (.alpha.S)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (2S)-2-(n-Propane-1-sulfonylamino)-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid tert-butyl ester
FS STEREOSEARCH
MF C25 H39 N9 O5 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

Searched by: Mary Hale 308-4258 CM-1 1E01



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 134:71601 Substituted purine derivatives, method of preparation and use as inhibitors of cell adhesion. Knolle, Jochen; Peyman, Anuschirwan; Gourvest, Jean-Francois; Ruxer, Jean-Marie; Gadek, Thomas R. (Aventis Pharma Deutschland G.m.b.H., Germany; Genentech, Inc.). Eur. Pat. Appl. EP 1065208 A1 20010103, 41 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 1999-112637 19990702.

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

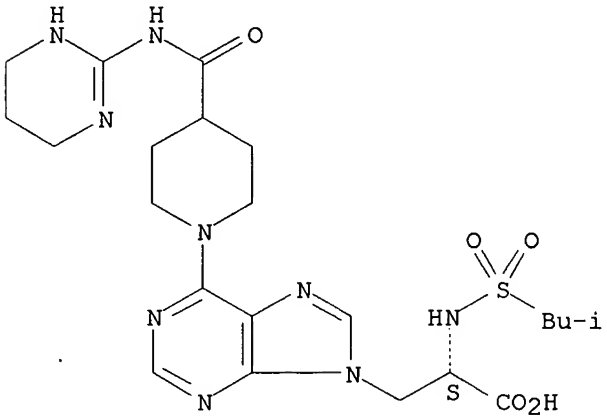
AB The present invention relates to purine derivs. I. B is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl, (C5-C14)heteroaryl-(C1-C8)alkyl, F, Cl, Br, OH, CN, CF3, NO2, CO2H, (C1-C6)alkoxy, (C1-C6)alkoxy-(C1-C6)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C5-C14)arylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C1-C6)alkylsulfonylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, aminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl or (C5-C14)heteroaryl, where all residues B are independent of one another and can be identical or different, or B denotes an arom. or nonarom. ring system that is fused to the 6-membered ring contg. the groups G and Z. D is -C(O)-N(R6)-, -NR6-C(O)-, -NR6-C(O)-N(R6)-, -NR6-C(S)-N(R6)-, -C(S)-N(R6)- or -C(R6):N-N(R6)-, where the divalent residues representing D are bonded to the group E via the free bond on their right side. E is a residue from the series consisting of possibly substituted 2-pyrimidinyl, pyrrolyl, 2-imidazolyl, 2-imidazolin-2-yl, 2-pyridinyl many other N heterocycles, R6-C(:NR6)-NR6-, and R6R6'N-C(:NR6)-. G is N, CH or C((C1-C4)alkyl). X is H, -NR6R6', F, Cl, Br, -OR6, -SR6, hydroxy-(C1-C6)alkyl-NH-, (hydroxy-(C1-C6)alkyl)2N-, amino-(C1-C6)alkyl-NH-

, (amino-(C1-C6)alkyl)2N-, hydroxy-(C1-C6)alkyl-O-, hydroxy-(C1-C6)alkyl-S- or -NH-C(O)-R6. Y has one of the meanings of R6 or is F, Cl, Br, CN, -NR6R6', -OR6, -SR6 or hydroxy-(C1-C6)alkyl-NH-. Z is N or CH. R1 is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl or (C5-C14)heteroaryl-(C1-C8)alkyl, where aryl, heteroaryl, cycloalkyl and alkyl can be substituted one, two or three times by identical or different substituents from the series consisting of F, Cl, Br, CN, CF3, NO2, CO2H, (C1-C6)alkyl, (C1-C6)alkoxy, (C1-C6)alkoxy-(C1-C8)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, (C1-C6)alkylaminosulfonyl, (C5-C14)arylaminosulfonyl, (C5-C14)aryl-(C1-C8)alkylaminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl and (C5-C14)heteroaryl. R2 is -C(O)R5, -C(S)R5, -S(O)pR5, -P(O)R5R5' or a residue of a 4-membered to 8-membered satd. or unsatd. heterocycle which contains 1-4 heteroatoms from the series consisting of N, O and S. R5 and R5' are OH, (C1-C8)alkoxy, (C5-C14)aryl-(C1-C8)alkoxy, (C1-C8)alkylcarbonyloxy-(C1-C4)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyloxy(C1-C8)alkoxy- or -NR6R6', where the residues R5' and R5' are independent of one another and can be identical or different. R6 and R6' are H, (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl where in the aryl residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or (C5-C14)aryl-(C1-C8)alkyl, where in the aryl moiety of the arylalkyl residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or R6 and R6' together with the N atom to which they are bonded form a 4-8-membered ring system which in addn. to the N atom to which R6 and R6' are bonded can contain 1-3 ring heteroatoms N, O and S and which can be unsatd. or satd., where all residues R6 and R6' are independent of one another and can be identical or different. R = 0-4; s = 0-4; v = 1-3; p = 1-2. The present invention also relates to stereoisomeric forms and mixts. thereof in all ratios, and their physiol. tolerable salts and their prodrugs; where, instead of the purine structure shown in I, also a 3-deazapurine structure, a 7-deazapurine structure or a 7-deaza-8-azapurine structure can be present. I are valuable pharmacol. active compds. They are vitronectin receptor antagonists and inhibitors of cell adhesion and are suitable for the therapy and prophylaxis of illnesses which are based on the interaction between vitronectin receptors and their ligands in cell-cell or cell-matrix interaction processes or which can be prevented, alleviated or cured by influencing such interactions. For example, they can be applied for inhibiting bone resorption by osteoclasts and thus for treating and preventing osteoporosis, or for inhibiting undesired angiogenesis or proliferation of cells of the vascular smooth musculature. The invention furthermore relates to processes for the prepn. of I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical compns. comprising them. The process for the prepn. comprises reacting II (L1 = leaving group; R15 = R1SO2 or an amino protecting group) with III or IV; B, D, E, G, X, R2 and s are as defined above but functional groups can also be present in the form of precursor groups or in protected form. For example, (2S)-2-benzyloxycarbonylamino-3-(6-chloropurin-9-yl)propionic acid tert-Bu ester was reacted with piperidine-4-carboxylic acid in the presence of N,O-bis(trimethylsilyl)acetamide to give 1-(9-((2S)-2-benzyloxycarbonylamino-2-tert-butoxycarbonylethyl)purin-6-yl)piperidine-4-carboxylic acid, which was reacted with 2-amino-1,4,5,6-tetrahydropyrimidine hydrochloride to give (2S)-2-Benzyloxycarbonylamino-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid tert-Bu ester, which was deprotected at N, N-sulfonated

by various sulfonyl chlorides and hydrolyzed to give products such as (2S)-2-(naphthalene-1-sulfonylamino)-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid.

L3 ANSWER 8 OF 12 REGISTRY COPYRIGHT 2002 ACS
RN 315212-27-2 REGISTRY
CN 9H-Purine-9-propanoic acid, .alpha.-[[(2-methylpropyl)sulfonyl]amino]-6-[4-[[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]carbonyl]-1-piperidinyl]-, (.alpha.S)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (2S)-2-(2-Methylpropane-1-sulfonylamino)-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid
FS STEREOSEARCH
MF C22 H33 N9 O5 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 134:71601 Substituted purine derivatives, method of preparation and use as inhibitors of cell adhesion. Knolle, Jochen; Peyman, Anuschirwan; Gourvest, Jean-Francois; Ruxer, Jean-Marie; Gadek, Thomas R. (Aventis Pharma Deutschland G.m.b.H., Germany; Genentech, Inc.). Eur. Pat. Appl. EP 1065208 A1 20010103, 41 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 1999-112637 19990702.
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention relates to purine derivs. I. B is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl, (C5-C14)heteroaryl-(C1-C8)alkyl, F, Cl, Br, OH, CN, CF3, NO2, CO2H, (C1-C6)alkoxy,

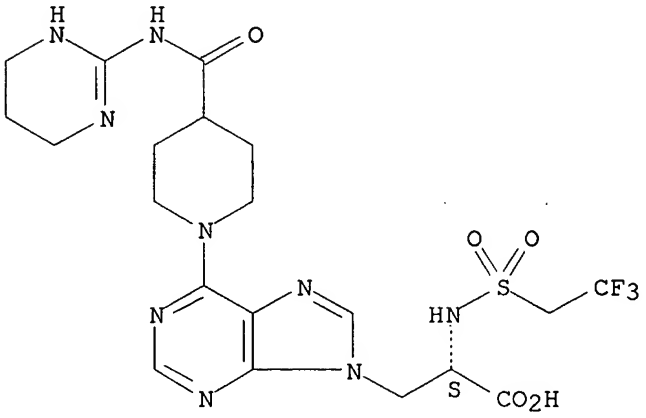
Searched by: Mary Hale 308-4258 CM-1 1E01

(C1-C6)alkoxy-(C1-C6)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C5-C14)arylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C1-C6)alkylsulfonylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, aminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl or (C5-C14)heteroaryl, where all residues B are independent of one another and can be identical or different, or B denotes an arom. or nonarom. ring system that is fused to the 6-membered ring contg. the groups G and Z. D is -C(O)-N(R6)-, -NR6-C(O)-, -NR6-C(O)-N(R6)-, -NR6-C(S)-N(R6)-, -C(S)-N(R6)- or -C(R6):N-N(R6)-, where the divalent residues representing D are bonded to the group E via the free bond on their right side. E is a residue from the series consisting of possibly substituted 2-pyrimidinyl, pyrrolyl, 2-imidazolyl, 2-imidazolin-2-yl, 2-pyridinyl many other N heterocycles, R6-C(:NR6)-NR6-, and R6R6'N-C(:NR6)-. G is N, CH or C((C1-C4)alkyl). X is H, -NR6R6', F, Cl, Br, -OR6, -SR6, hydroxy-(C1-C6)alkyl-NH-, (hydroxy-(C1-C6)alkyl)2N-, amino-(C1-C6)alkyl-NH-, (amino-(C1-C6)alkyl)2N-, hydroxy-(C1-C6)alkyl-O-, hydroxy-(C1-C6)alkyl-S- or -NH-C(O)-R6. Y has one of the meanings of R6 or is F, Cl, Br, CN, -NR6R6', -OR6, -SR6 or hydroxy-(C1-C6)alkyl-NH-. Z is N or CH. R1 is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl or (C5-C14)heteroaryl-(C1-C8)alkyl, where aryl, heteroaryl, cycloalkyl and alkyl can be substituted one, two or three times by identical or different substituents from the series consisting of F, Cl, Br, CN, CF3, NO2, CO2H, (C1-C6)alkyl, (C1-C6)alkoxy, (C1-C6)alkoxy-(C1-C8)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, (C1-C6)alkylaminosulfonyl, (C5-C14)arylaminosulfonyl, (C5-C14)aryl-(C1-C8)alkylaminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl and (C5-C14)heteroaryl. R2 is -C(O)R5, -C(S)R5, -S(O)pR5, -P(O)R5R5' or a residue of a 4-membered to 8-membered satd. or unsatd. heterocycle which contains 1-4 heteroatoms from the series consisting of N, O and S. R5 and R5' are OH, (C1-C8)alkoxy, (C5-C14)aryl-(C1-C8)alkoxy, (C1-C8)alkylcarbonyloxy-(C1-C4)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyloxy(C1-C8)alkoxy- or -NR6R6', where the residues R5' and R5' are independent of one another and can be identical or different. R6 and R6' are H, (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl where in the aryl residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or (C5-C14)aryl-(C1-C8)alkyl, where in the aryl moiety of the arylalkyl residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or R6 and R6' together with the N atom to which they are bonded form a 4-8-membered ring system which in addn. to the N atom to which R6 and R6' are bonded can contain 1-3 ring heteroatoms N, O and S and which can be unsatd. or satd., where all residues R6 and R6' are independent of one another and can be identical or different. R = 0-4; s = 0-4; v = 1-3; p = 1-2. The present invention also relates to stereoisomeric forms and mixts. thereof in all ratios, and their physiol. tolerable salts and their prodrugs; where, instead of the purine structure shown in I, also a 3-deazapurine structure, a 7-deazapurine structure or a 7-deaza-8-azapurine structure can be present. I are valuable pharmacol. active compds. They are vitronectin receptor antagonists and inhibitors of cell adhesion and are suitable for the therapy and prophylaxis of illnesses which are based on the interaction between vitronectin receptors and their ligands in cell-cell or cell-matrix interaction processes or which can be prevented, alleviated or cured by influencing such interactions. For example, they can be applied for inhibiting bone

resorption by osteoclasts and thus for treating and preventing osteoporosis, or for inhibiting undesired angiogenesis or proliferation of cells of the vascular smooth musculature. The invention furthermore relates to processes for the prepn. of I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical compns. comprising them. The process for the prepn. comprises reacting II (L1 = leaving group; R15 = R1SO2 or an amino protecting group) with III or IV; B, D, E, G, X, R2 and s are as defined above but functional groups can also be present in the form of precursor groups or in protected form. For example, (2S)-2-benzyloxycarbonylamino-3-(6-chloropurin-9-yl)propionic acid tert-Bu ester was reacted with piperidine-4-carboxylic acid in the presence of N,O-bis(trimethylsilyl)acetamide to give 1-(9-((2S)-2-benzyloxycarbonylamino-2-tert-butoxycarbonylethyl)purin-6-yl)piperidine-4-carboxylic acid, which was reacted with 2-amino-1,4,5,6-tetrahydropyrimidine hydrochloride to give (2S)-2-Benzyloxycarbonylamino-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid tert-Bu ester, which was deprotected at N, N-sulfonated by various sulfonyl chlorides and hydrolyzed to give products such as (2S)-2-(naphthalene-1-sulfonylamino)-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid.

L3 ANSWER 9 OF 12 REGISTRY COPYRIGHT 2002 ACS
RN 315212-26-1 REGISTRY
CN 9H-Purine-9-propanoic acid, 6-[4-[[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]carbonyl]-1-piperidinyl]-.alpha.-[[(2,2,2-trifluoroethyl)sulfonyl]amino]-, (.alpha.S)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (2S)-3-(6-(4-(1,4,5,6-Tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)-2-(2,2,2-trifluoroethanesulfonylamino)propionic acid
FS STEREOSEARCH
MF C20 H26 F3 N9 O5 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 134:71601 Substituted purine derivatives, method of preparation

Searched by: Mary Hale 308-4258 CM-1 1E01

and use as inhibitors of cell adhesion. Knolle, Jochen; Peyman, Anuschirwan; Gourvest, Jean-Francois; Ruxer, Jean-Marie; Gadek, Thomas R. (Aventis Pharma Deutschland G.m.b.H., Germany; Genentech, Inc.). Eur. Pat. Appl. EP 1065208 A1 20010103, 41 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 1999-112637 19990702.

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

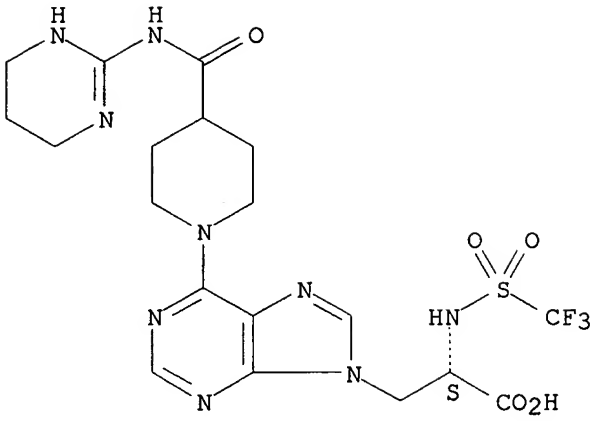
AB The present invention relates to purine derivs. I. B is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl, (C5-C14)heteroaryl-(C1-C8)alkyl, F, Cl, Br, OH, CN, CF3, NO2, CO2H, (C1-C6)alkoxy, (C1-C6)alkoxy-(C1-C6)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C5-C14)arylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C1-C6)alkylsulfonylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, aminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl or (C5-C14)heteroaryl, where all residues B are independent of one another and can be identical or different, or B denotes an arom. or nonarom. ring system that is fused to the 6-membered ring contg. the groups G and Z. D is -C(O)-N(R6)-, -NR6-C(O)-, -NR6-C(O)-N(R6)-, -NR6-C(S)-N(R6)-, -C(S)-N(R6)- or -C(R6):N-N(R6)-, where the divalent residues representing D are bonded to the group E via the free bond on their right side. E is a residue from the series consisting of possibly substituted 2-pyrimidinyl, pyrrolyl, 2-imidazolyl, 2-imidazolin-2-yl, 2-pyridinyl many other N heterocycles, R6-C(:NR6)-NR6-, and R6R6'N-C(:NR6)-. G is N, CH or C((C1-C4)alkyl). X is H, -NR6R6', F, Cl, Br, -OR6, -SR6, hydroxy-(C1-C6)alkyl-NH-, (hydroxy-(C1-C6)alkyl)2N-, amino-(C1-C6)alkyl-NH-, (amino-(C1-C6)alkyl)2N-, hydroxy-(C1-C6)alkyl-O-, hydroxy-(C1-C6)alkyl-S- or -NH-C(O)-R6. Y has one of the meanings of R6 or is F, Cl, Br, CN, -NR6R6', -OR6, -SR6 or hydroxy-(C1-C6)alkyl-NH-. Z is N or CH. R1 is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl or (C5-C14)heteroaryl-(C1-C8)alkyl, where aryl, heteroaryl, cycloalkyl and alkyl can be substituted one, two or three times by identical or different substituents from the series consisting of F, Cl, Br, CN, CF3, NO2, CO2H, (C1-C6)alkyl, (C1-C6)alkoxy, (C1-C6)alkoxy-(C1-C8)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, (C1-C6)alkylaminosulfonyl, (C5-C14)arylaminosulfonyl, (C5-C14)aryl-(C1-C8)alkylaminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl and (C5-C14)heteroaryl. R2 is -C(O)R5, -C(S)R5, -S(O)pR5, -P(O)R5R5' or a residue of a 4-membered to 8-membered satd. or unsatd. heterocycle which contains 1-4 heteroatoms from the series consisting of N, O and S. R5 and R5' are OH, (C1-C8)alkoxy, (C5-C14)aryl-(C1-C8)alkoxy, (C1-C8)alkylcarbonyloxy-(C1-C4)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyloxy(C1-C8)alkoxy- or -NR6R6', where the residues R5' and R5' are independent of one another and can be identical or different. R6 and R6' are H, (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl where in the aryl residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or (C5-C14)aryl-(C1-C8)alkyl, where in

the aryl moiety of the arylalkyl residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or R6 and R6' together with the N atom to which they are bonded form a 4-8-membered ring system which in addn. to the N atom to which R6 and R6' are bonded can contain 1-3 ring heteroatoms N, O and S and which can be unsatd. or satd., where all residues R6 and R6' are independent of one another and can be identical or different. R = 0-4; s = 0-4; v = 1-3; p = 1-2. The present invention also relates to stereoisomeric forms and mixts. thereof in all ratios, and their physiol. tolerable salts and their prodrugs; where, instead of the purine structure shown in I, also a 3-deazapurine structure, a 7-deazapurine structure or a 7-deaza-8-azapurine structure can be present. I are valuable pharmacol. active compds. They are vitronectin receptor antagonists and inhibitors of cell adhesion and are suitable for the therapy and prophylaxis of illnesses which are based on the interaction between vitronectin receptors and their ligands in cell-cell or cell-matrix interaction processes or which can be prevented, alleviated or cured by influencing such interactions. For example, they can be applied for inhibiting bone resorption by osteoclasts and thus for treating and preventing osteoporosis, or for inhibiting undesired angiogenesis or proliferation of cells of the vascular smooth musculature. The invention furthermore relates to processes for the prepn. of I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical compns. comprising them. The process for the prepn. comprises reacting II (L1 = leaving group; R15 = R1SO2 or an amino protecting group) with III or IV; B, D, E, G, X, R2 and s are as defined above but functional groups can also be present in the form of precursor groups or in protected form. For example, (2S)-2-benzyloxycarbonylamino-3-(6-chloropurin-9-yl)propionic acid tert-Bu ester was reacted with piperidine-4-carboxylic acid in the presence of N,O-bis(trimethylsilyl)acetamide to give 1-(9-((2S)-2-benzyloxycarbonylamino-2-tert-butoxycarbonylethyl)purin-6-yl)piperidine-4-carboxylic acid, which was reacted with 2-amino-1,4,5,6-tetrahydropyrimidine hydrochloride to give (2S)-2-Benzyloxycarbonylamino-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid tert-Bu ester, which was deprotected at N, N-sulfonated by various sulfonyl chlorides and hydrolyzed to give products such as (2S)-2-(naphthalene-1-sulfonylamino)-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid.

L3 ANSWER 10 OF 12 REGISTRY COPYRIGHT 2002 ACS
RN 315212-25-0 REGISTRY
CN 9H-Purine-9-propanoic acid, 6-[4-[[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]carbonyl]-1-piperidinyl]-.alpha.-[[(trifluoromethyl)sulfonyl]amino]-, (.alpha.S)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (2S)-3-(6-(4-(1,4,5,6-Tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)-2-trifluoromethanesulfonylaminopropionic acid
FS STEREOSEARCH
MF C19 H24 F3 N9 O5 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

Searched by: Mary Hale 308-4258 CM-1 1E01



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 134:71601 Substituted purine derivatives, method of preparation and use as inhibitors of cell adhesion. Knolle, Jochen; Peyman, Anuschirwan; Gourvest, Jean-Francois; Ruxer, Jean-Marie; Gadek, Thomas R. (Aventis Pharma Deutschland G.m.b.H., Germany; Genentech, Inc.). Eur. Pat. Appl. EP 1065208 A1 20010103, 41 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 1999-112637 19990702.

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention relates to purine derivs. I. B is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl, (C5-C14)heteroaryl-(C1-C8)alkyl, F, Cl, Br, OH, CN, CF3, NO2, CO2H, (C1-C6)alkoxy, (C1-C6)alkoxy-(C1-C6)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C5-C14)arylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C1-C6)alkylsulfonylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, aminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl or (C5-C14)heteroaryl, where all residues B are independent of one another and can be identical or different, or B denotes an arom. or nonarom. ring system that is fused to the 6-membered ring contg. the groups G and Z. D is -C(O)-N(R6)-, -NR6-C(O)-, -NR6-C(O)-N(R6)-, -NR6-C(S)-N(R6)-, -C(S)-N(R6)- or -C(R6):N-N(R6)-, where the divalent residues representing D are bonded to the group E via the free bond on their right side. E is a residue from the series consisting of possibly substituted 2-pyrimidinyl, pyrrolyl, 2-imidazolyl, 2-imidazolin-2-yl, 2-pyridinyl many other N heterocycles, R6-C(:NR6)-NR6-, and R6R6'N-C(:NR6)-. G is N, CH or C((C1-C4)alkyl). X is H, -NR6R6', F, Cl, Br, -OR6, -SR6, hydroxy-(C1-C6)alkyl-NH-, (hydroxy-(C1-C6)alkyl)2N-, amino-(C1-C6)alkyl-NH-, (amino-(C1-C6)alkyl)2N-, hydroxy-(C1-C6)alkyl-O-, hydroxy-(C1-C6)alkyl-S-

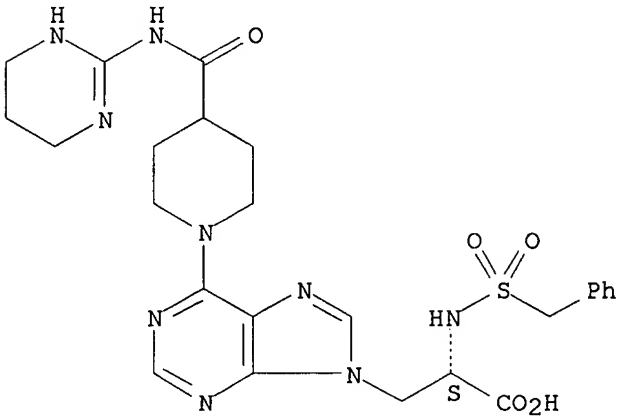
Searched by: Mary Hale 308-4258 CM-1 1E01

or -NH-C(O)-R6. Y has one of the meanings of R6 or is F, Cl, Br, CN, -NR6R6', -OR6, -SR6 or hydroxy-(C1-C6)alkyl-NH-. Z is N or CH. R1 is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl or (C5-C14)heteroaryl-(C1-C8)alkyl, where aryl, heteroaryl, cycloalkyl and alkyl can be substituted one, two or three times by identical or different substituents from the series consisting of F, Cl, Br, CN, CF3, NO2, CO2H, (C1-C6)alkyl, (C1-C6)alkoxy, (C1-C6)alkoxy-(C1-C8)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, (C1-C6)alkylaminosulfonyl, (C5-C14)arylaminosulfonyl, (C5-C14)aryl-(C1-C8)alkylaminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl and (C5-C14)heteroaryl. R2 is -C(O)R5, -C(S)R5, -S(O)pR5, -P(O)R5R5' or a residue of a 4-membered to 8-membered satd. or unsatd. heterocycle which contains 1-4 heteroatoms from the series consisting of N, O and S. R5 and R5' are OH, (C1-C8)alkoxy, (C5-C14)aryl-(C1-C8)alkoxy, (C1-C8)alkylcarbonyloxy-(C1-C4)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyloxy(C1-C8)alkoxy- or -NR6R6', where the residues R5' and R5' are independent of one another and can be identical or different. R6 and R6' are H, (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl where in the aryl residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or (C5-C14)aryl-(C1-C8)alkyl, where in the aryl moiety of the arylalkyl residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or R6 and R6' together with the N atom to which they are bonded form a 4-8-membered ring system which in addn. to the N atom to which R6 and R6' are bonded can contain 1-3 ring heteroatoms N, O and S and which can be unsatd. or satd., where all residues R6 and R6' are independent of one another and can be identical or different. R = 0-4; s = 0-4; v = 1-3; p = 1-2. The present invention also relates to stereoisomeric forms and mixts. thereof in all ratios, and their physiol. tolerable salts and their prodrugs; where, instead of the purine structure shown in I, also a 3-deazapurine structure, a 7-deazapurine structure or a 7-deaza-8-azapurine structure can be present. I are valuable pharmacol. active compds. They are vitronectin receptor antagonists and inhibitors of cell adhesion and are suitable for the therapy and prophylaxis of illnesses which are based on the interaction between vitronectin receptors and their ligands in cell-cell or cell-matrix interaction processes or which can be prevented, alleviated or cured by influencing such interactions. For example, they can be applied for inhibiting bone resorption by osteoclasts and thus for treating and preventing osteoporosis, or for inhibiting undesired angiogenesis or proliferation of cells of the vascular smooth musculature. The invention furthermore relates to processes for the prepn. of I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical compns. comprising them. The process for the prepn. comprises reacting II (L1 = leaving group; R15 = R1SO2 or an amino protecting group) with III or IV; B, D, E, G, X, R2 and s are as defined above but functional groups can also be present in the form of precursor groups or in protected form. For example, (2S)-2-benzyloxycarbonylamino-3-(6-chloropurin-9-yl)propionic acid tert-Bu ester was reacted with piperidine-4-carboxylic acid in the presence of N,O-bis(trimethylsilyl)acetamide to give 1-(9-((2S)-2-benzyloxycarbonylamino-2-tert-butoxycarbonylethyl)purin-6-yl)piperidine-4-carboxylic acid, which was reacted with 2-amino-1,4,5,6-tetrahydropyrimidine hydrochloride to give (2S)-2-Benzyloxycarbonylamino-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid tert-Bu ester, which was deprotected at N, N-sulfonated by various sulfonyl chlorides and hydrolyzed to give products such as

(2S)-2-(naphthalene-1-sulfonylamino)-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid.

L3 ANSWER 11 OF 12 REGISTRY COPYRIGHT 2002 ACS
RN 315212-24-9 REGISTRY
CN 9H-Purine-9-propanoic acid, .alpha.-[[(phenylmethyl)sulfonyl]amino]-6-[4-[[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]carbonyl]-1-piperidinyl]-, (.alpha.S)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (2S)-2-Phenylmethanesulfonylamino-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid
FS STEREOSEARCH
MF C25 H31 N9 O5 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 134:71601 Substituted purine derivatives, method of preparation and use as inhibitors of cell adhesion. Knolle, Jochen; Peyman, Anuschirwan; Gourvest, Jean-Francois; Ruxer, Jean-Marie; Gadek, Thomas R. (Aventis Pharma Deutschland G.m.b.H., Germany; Genentech, Inc.). Eur. Pat. Appl. EP 1065208 A1 20010103, 41 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 1999-112637 19990702.
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention relates to purine derivs. I. B is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl, (C5-C14)heteroaryl-(C1-C8)alkyl, F, Cl, Br, OH, CN, CF3, NO2, CO2H, (C1-C6)alkoxy, (C1-C6)alkoxy-(C1-C6)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl,

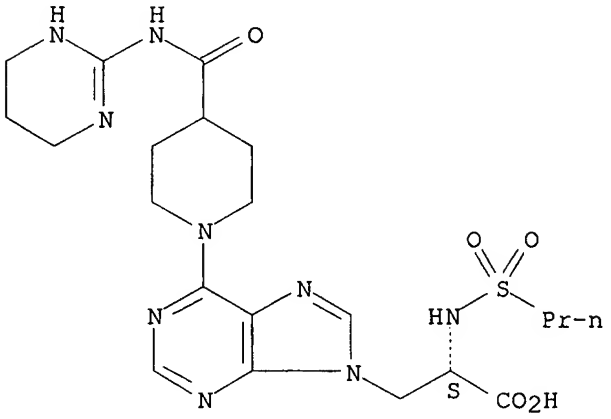
Searched by: Mary Hale 308-4258 CM-1 1E01

(C5-C14)arylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C1-C6)alkylsulfonylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, aminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl or (C5-C14)heteroaryl, where all residues B are independent of one another and can be identical or different, or B denotes an arom. or nonarom. ring system that is fused to the 6-membered ring contg. the groups G and Z. D is -C(O)-N(R6)-, -NR6-C(O)-, -NR6-C(O)-N(R6)-, -NR6-C(S)-N(R6)-, -C(S)-N(R6)- or -C(R6):N-N(R6)-, where the divalent residues representing D are bonded to the group E via the free bond on their right side. E is a residue from the series consisting of possibly substituted 2-pyrimidinyl, pyrrolyl, 2-imidazolyl, 2-imidazolin-2-yl, 2-pyridinyl many other N heterocycles, R6-C(:NR6)-NR6-, and R6R6'N-C(:NR6)-. G is N, CH or C((C1-C4)alkyl). X is H, -NR6R6', F, Cl, Br, -OR6, -SR6, hydroxy-(C1-C6)alkyl-NH-, (hydroxy-(C1-C6)alkyl)2N-, amino-(C1-C6)alkyl-NH-, (amino-(C1-C6)alkyl)2N-, hydroxy-(C1-C6)alkyl-O-, hydroxy-(C1-C6)alkyl-S- or -NH-C(O)-R6. Y has one of the meanings of R6 or is F, Cl, Br, CN, -NR6R6', -OR6, -SR6 or hydroxy-(C1-C6)alkyl-NH-. Z is N or CH. R1 is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl or (C5-C14)heteroaryl-(C1-C8)alkyl, where aryl, heteroaryl, cycloalkyl and alkyl can be substituted one, two or three times by identical or different substituents from the series consisting of F, Cl, Br, CN, CF3, NO2, CO2H, (C1-C6)alkyl, (C1-C6)alkoxy, (C1-C6)alkoxy-(C1-C8)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, (C1-C6)alkylaminosulfonyl, (C5-C14)arylaminosulfonyl, (C5-C14)aryl-(C1-C8)alkylaminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl and (C5-C14)heteroaryl. R2 is -C(O)R5, -C(S)R5, -S(O)pR5, -P(O)R5R5' or a residue of a 4-membered to 8-membered satd. or unsatd. heterocycle which contains 1-4 heteroatoms from the series consisting of N, O and S. R5 and R5' are OH, (C1-C8)alkoxy, (C5-C14)aryl-(C1-C8)alkoxy, (C1-C8)alkylcarbonyloxy-(C1-C4)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyloxy(C1-C8)alkoxy- or -NR6R6', where the residues R5' and R5' are independent of one another and can be identical or different. R6 and R6' are H, (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl where in the aryl residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or (C5-C14)aryl-(C1-C8)alkyl, where in the aryl moiety of the arylalkyl residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or R6 and R6' together with the N atom to which they are bonded form a 4-8-membered ring system which in addn. to the N atom to which R6 and R6' are bonded can contain 1-3 ring heteroatoms N, O and S and which can be unsatd. or satd., where all residues R6 and R6' are independent of one another and can be identical or different. R = 0-4; s = 0-4; v = 1-3; p = 1-2. The present invention also relates to stereoisomeric forms and mixts. thereof in all ratios, and their physiol. tolerable salts and their prodrugs; where, instead of the purine structure shown in I, also a 3-deazapurine structure, a 7-deazapurine structure or a 7-deaza-8-azapurine structure can be present. I are valuable pharmacol. active compds. They are vitronectin receptor antagonists and inhibitors of cell adhesion and are suitable for the therapy and prophylaxis of illnesses which are based on the interaction between vitronectin receptors and their ligands in cell-cell or cell-matrix interaction processes or which can be prevented, alleviated or cured by influencing such interactions. For example, they can be applied for inhibiting bone resorption by osteoclasts and thus for treating and preventing

osteoporosis, or for inhibiting undesired angiogenesis or proliferation of cells of the vascular smooth musculature. The invention furthermore relates to processes for the prepn. of I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical compns. comprising them. The process for the prepn. comprises reacting II (L1 = leaving group; R15 = R1SO2 or an amino protecting group) with III or IV; B, D, E, G, X, R2 and s are as defined above but functional groups can also be present in the form of precursor groups or in protected form. For example, (2S)-2-benzyloxycarbonylamino-3-(6-chloropurin-9-yl)propionic acid tert-Bu ester was reacted with piperidine-4-carboxylic acid in the presence of N,O-bis(trimethylsilyl)acetamide to give 1-(9-((2S)-2-benzyloxycarbonylamino-2-tert-butoxycarbonylethyl)purin-6-yl)piperidine-4-carboxylic acid, which was reacted with 2-amino-1,4,5,6-tetrahydropyrimidine hydrochloride to give (2S)-2-Benzyloxycarbonylamino-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid tert-Bu ester, which was deprotected at N, N-sulfonated by various sulfonyl chlorides and hydrolyzed to give products such as (2S)-2-(naphthalene-1-sulfonylamino)-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid.

L3 ANSWER 12 OF 12 REGISTRY COPYRIGHT 2002 ACS
RN 315212-21-6 REGISTRY
CN 9H-Purine-9-propanoic acid, .alpha.-[(propylsulfonyl)amino]-6-[4-[[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]carbonyl]-1-piperidinyl]-, (.alpha.S)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (2S)-2-(Propane-1-sulfonylamino)-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid
FS STEREOSEARCH
MF C21 H31 N9 O5 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 134:71601 Substituted purine derivatives, method of preparation and use as inhibitors of cell adhesion. Knolle, Jochen; Peyman,

Searched by: Mary Hale 308-4258 CM-1 1E01

Anuschirwan; Gourvest, Jean-Francois; Ruxer, Jean-Marie; Gadek, Thomas R. (Aventis Pharma Deutschland G.m.b.H., Germany; Genentech, Inc.). Eur. Pat. Appl. EP 1065208 A1 20010103, 41 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 1999-112637 19990702.

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention relates to purine derivs. I. B is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl, (C5-C14)heteroaryl-(C1-C8)alkyl, F, Cl, Br, OH, CN, CF3, NO2, CO2H, (C1-C6)alkoxy, (C1-C6)alkoxy-(C1-C6)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C5-C14)arylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C1-C6)alkylsulfonylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, aminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl or (C5-C14)heteroaryl, where all residues B are independent of one another and can be identical or different, or B denotes an arom. or nonarom. ring system that is fused to the 6-membered ring contg. the groups G and Z. D is -C(O)-N(R6)-, -NR6-C(O)-, -NR6-C(O)-N(R6)-, -NR6-C(S)-N(R6)-, -C(S)-N(R6)- or -C(R6):N-N(R6)-, where the divalent residues representing D are bonded to the group E via the free bond on their right side. E is a residue from the series consisting of possibly substituted 2-pyrimidinyl, pyrrolyl, 2-imidazolyl, 2-imidazolin-2-yl, 2-pyridinyl many other N heterocycles, R6-C(:NR6)-NR6-, and R6R6'N-C(:NR6)-. G is N, CH or C((C1-C4)alkyl). X is H, -NR6R6', F, Cl, Br, -OR6, -SR6, hydroxy-(C1-C6)alkyl-NH-, (hydroxy-(C1-C6)alkyl)2N-, amino-(C1-C6)alkyl-NH-, (amino-(C1-C6)alkyl)2N-, hydroxy-(C1-C6)alkyl-O-, hydroxy-(C1-C6)alkyl-S- or -NH-C(O)-R6. Y has one of the meanings of R6 or is F, Cl, Br, CN, -NR6R6', -OR6, -SR6 or hydroxy-(C1-C6)alkyl-NH-. Z is N or CH. R1 is (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl, (C5-C14)aryl-(C1-C8)alkyl, (C5-C14)heteroaryl or (C5-C14)heteroaryl-(C1-C8)alkyl, where aryl, heteroaryl, cycloalkyl and alkyl can be substituted one, two or three times by identical or different substituents from the series consisting of F, Cl, Br, CN, CF3, NO2, CO2H, (C1-C6)alkyl, (C1-C6)alkoxy, (C1-C6)alkoxy-(C1-C8)alkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C1-C6)alkylaminocarbonyl, (C1-C6)alkoxy-(C1-C6)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyl, (C1-C6)alkanoylamino, (C5-C14)arylsulfonylamino, (C1-C6)alkylsulfonylamino, (C1-C6)alkylamino, di((C1-C6)alkyl)amino, (C1-C6)alkylsulfonyl, (C1-C6)alkylaminosulfonyl, (C5-C14)arylaminosulfonyl, (C5-C14)aryl-(C1-C8)alkylaminosulfonyl, (C5-C14)arylsulfonyl, (C5-C14)aryl-(C1-C8)alkylsulfonyl, (C5-C14)aryl and (C5-C14)heteroaryl. R2 is -C(O)R5, -C(S)R5, -S(O)pR5, -P(O)R5R5' or a residue of a 4-membered to 8-membered satd. or unsatd. heterocycle which contains 1-4 heteroatoms from the series consisting of N, O and S. R5 and R5' are OH, (C1-C8)alkoxy, (C5-C14)aryl-(C1-C8)alkoxy, (C1-C8)alkylcarbonyloxy-(C1-C4)alkoxy, (C5-C14)aryl-(C1-C8)alkylcarbonyloxy(C1-C8)alkoxy- or -NR6R6', where the residues R5' and R5' are independent of one another and can be identical or different. R6 and R6' are H, (C1-C18)alkyl, (C3-C14)cycloalkyl, (C3-C14)cycloalkyl-(C1-C8)alkyl, (C5-C14)aryl where in the aryl residue 1-5 ring C atoms can be replaced by heteroatoms N, O and S, or (C5-C14)aryl-(C1-C8)alkyl, where in the aryl moiety of the arylalkyl residue 1-5 ring C atoms can be replaced

by heteroatoms N, O and S, or R6 and R6' together with the N atom to which they are bonded form a 4-8-membered ring system which in addn. to the N atom to which R6 and R6' are bonded can contain 1-3 ring heteroatoms N, O and S and which can be unsatd. or satd., where all residues R6 and R6' are independent of one another and can be identical or different. R = 0-4; s = 0-4; v = 1-3; p = 1-2. The present invention also relates to stereoisomeric forms and mixts. thereof in all ratios, and their physiol. tolerable salts and their prodrugs; where, instead of the purine structure shown in I, also a 3-deazapurine structure, a 7-deazapurine structure or a 7-deaza-8-azapurine structure can be present. I are valuable pharmacol. active compds. They are vitronectin receptor antagonists and inhibitors of cell adhesion and are suitable for the therapy and prophylaxis of illnesses which are based on the interaction between vitronectin receptors and their ligands in cell-cell or cell-matrix interaction processes or which can be prevented, alleviated or cured by influencing such interactions. For example, they can be applied for inhibiting bone resorption by osteoclasts and thus for treating and preventing osteoporosis, or for inhibiting undesired angiogenesis or proliferation of cells of the vascular smooth musculature. The invention furthermore relates to processes for the prepn. of I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical compns. comprising them. The process for the prepn. comprises reacting II (L1 = leaving group; R15 = R1SO2 or an amino protecting group) with III or IV; B, D, E, G, X, R2 and s are as defined above but functional groups can also be present in the form of precursor groups or in protected form. For example, (2S)-2-benzyloxycarbonylamino-3-(6-chloropurin-9-yl)propionic acid tert-Bu ester was reacted with piperidine-4-carboxylic acid in the presence of N,O-bis(trimethylsilyl)acetamide to give 1-(9-((2S)-2-benzyloxycarbonylamino-2-tert-butoxycarbonylethyl)purin-6-yl)piperidine-4-carboxylic acid, which was reacted with 2-amino-1,4,5,6-tetrahydropyrimidine hydrochloride to give (2S)-2-Benzyloxycarbonylamino-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid tert-Bu ester, which was deprotected at N, N-sulfonated by various sulfonyl chlorides and hydrolyzed to give products such as (2S)-2-(naphthalene-1-sulfonylamino)-3-(6-(4-(1,4,5,6-tetrahydropyrimidin-2-ylcarbamoyl)piperidin-1-yl)purin-9-yl)propionic acid.

=> fil caol;s l3

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	186.92	444.10

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-7.08	-7.08

FILE 'CAOLD' ENTERED AT 08:05:58 ON 04 NOV 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE

Searched by: Mary Hale 308-4258 CM-1 1E01

display formats.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

L4 0 L3

=> del his y